REMARKS

Claims 1-7, 17-20, 31, and 36-37 are canceled. Applicants reserve the right to pursue any canceled subject matter in one or more continuation, divisional, or continuation-in-part applications.

Claims 8-16, 21-30, 32-35, and 38 are pending. Claims 8-16, 21-30, and 32-24 are withdrawn by the Examiner according to the Restriction Requirement dated June 26, 2006, and made final in the Office Action dated October 19, 2007. Claims 35 and 38 are examined.

Rejection Under 35 U.S.C. § 101

Claims 35 and 38 are rejected under 35 U.S.C. § 101 for failing to support either a specific, substantial and credible asserted utility or a well-established utility. Applicants respectfully traverse on the basis that the transgenic mouse according to claim 35 and the cells according to claim 38 have a specific, substantial and credible asserted utility in screening for compounds that have the same activity as SEQ ID NO:5 (*i.e.* putative agonists of TLR9), where SEQ ID NO: 5 is known in the art to have therapeutic value against infection, for example, infection with *Leishmania major*.

Legal Standard for Utility

The legal standard for utility has been set forth by the Supreme Court, which stated:

> The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point - where specific benefit exists in currently available form - there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

Brenner v. Manson, 383 U.S. 519, 534-535 (1966). Consequently, it is well established that a patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered. In addition to providing a substantial utility, an asserted use must also be specific, i.e., it must "show that the claimed invention can be used to provide a well-defined and particular benefit to the public" (see *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005)).

The USPTO's own guidelines affirm that research tools used in a research or laboratory setting can have utility:

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

(see MPEP, § 2107.01 I C). With respect to the USPTO's utility guidelines, the Federal Circuit has stated that "[t]he PTO's standards for assessing whether a claimed invention has a specific and substantial utility comport with this court's interpretation of the utility requirement of § 101" (see *Fisher* at 1371).

Utility in Screening for Agonists of TLR9

A specific, substantial and credible utility for transgenic mice according to claim 35, and cells according to claim 38, is for screening for additional drugs with similar activity to SEQ ID NO:5, *i.e.* agonists of TLR9, where SEQ ID NO:5 is known in the art to have therapeutic value against infection, for example, infection with *Leishmania major*.

The specification discloses that knockout mice according to the invention are useful tools in evaluating agonists for TLR9. For example, the specification discloses that having

non-human animals lacking the specified gene function (i.e., knockout mice) and cells from such non-human animals:

> enables us to screen agonists or antagonists of the receptor proteins…. What is obtained by the screening may be suppressing or promoting substances against bacterial infected diseases.

(Specification, page 15, lines 9-10 and 14-19 [paragraph 0050 in published application]). In addition, the specification teaches that knockout mice and their cells according to the invention can be useful in developing "suppressing agents" (i.e. treatments) for bacterial infections. See, for example, page 14, lines 7-9 [paragraph 0047 in published application] and page 15, lines 18-20 [paragraph 0050 in published application]. Furthermore, the specification teaches that:

> Further, in evaluating and measuring the levels of macrophage activities or spleen cell activities, it is preferable to evaluate and compare them with the measurement values obtained from wild-type non-human animals, especially wild-type non-human animals born from the same parent to remove variances arising from individual differences. The same also applies to screening of suppressing or promoting substances reactive to bacterial DNA having an unmethylated CpG sequence shown below.

(See Specification, page 16, lines 14-19 [paragraph 0053 in published application]). Therefore, the specification teaches that knockout mice according to the invention, and their cells, are useful in screening for agonists of TLR9, which are useful in the treatment of bacterial infection.

Example 4 Demonstrates An Example Of Screening For Agonists For TLR9

In Experiment 4, the specification provides a specific example of screening for agonists of TLR9 which can be useful in the treatment of bacterial infection (see page 21, line 26 through page 23, line 29).

In the example, the specification compares the response of cells from wild-type and knockout mice according to the invention to SEQ ID NO.5, as shown in Figure 5. Specifically, the first three charts in Figure 5 show that wild-type cells respond to SEQ ID No. 5

by producing increasing levels of TNFα, IL-6, and IL-12 in a dose-response manner, i.e. increasing levels of SEQ ID NO.5 generally correspond to increasing levels of TNFα, IL-6, and IL-12. In other words, in the wild-type, SEQ ID NO.5 is shown to be an agonist causing an increased biological response. By comparison, the knockout mice cells have a response of "N.D." or not detected. The results show that the wild-type and knockout cells respond differently to SEQ ID NO.5, which provide valuable evidence that SEQ ID NO.5 is an agonist for the receptor that is lacking in the knockout animals which are accordingly unresponsive to SEQ ID NO.5. By having a negative screen available in the knockout mice according to the invention (**and only by having the knockout mice available**), the results for SEQ ID NO.5 as an agonist for TLR9 are validated.

The example also shows that wild-type and knockout cells "produce almost the same" response to LPS or PGN (see Figure 5). In the fourth chart in Figure 5, the response of wild-type and knockout mice cells are compared after dosage with either PGN or LPS. In both cases, the amount of TNFα produced is almost the same. In other words, the data in Figure 5 show that neither LPS nor PGN are agonists for TLR9. The result is important because it shows that, in general, LPS and PGN operate through a different mechanism than SEQ ID NO.5. Importantly, because of the different mechanisms for LPS and PGN compared to SEQ ID NO.5, one would generally predict that LPS and PGN have different biological effects *in vivo* from SEQ ID NO.5. By having a negative screen available in the knockout mice according to the invention (**and only by having the knockout mice available**), the results for LPS and PGN as not being agonists for TLR9 are validated.

The question answered by Example 4 is not whether a given agent will cause production of a certain level of TNFα. As seen in the data, all three agents (SEQ ID NO.5, PGN,

and LPS) can increase production of TNFα. Rather, the important question answered by the use of the knockout mice is whether two compounds operate via the same mechanism. The data in Figure 5 provides valuable evidence that PGN and LPS operate through a different mechanism than SEQ ID NO.5. In other words, Example 4 demonstrates a screen for agonists of TLR9, and shows that SEQ ID NO.5 is an agonist of TLR9, while LPS and PGN are not agonists of TLR9.

Extending the methodology of Example 4, the knockout mice and cells according to the invention are useful for screening putative agonists for TLR9 in a medicinal chemistry program for treatments of bacterial infection, as shown in Experiment 4. In other words, in the same way that a microscope or other analytical tool is used in a laboratory, knockout mice according to the invention are a desired and useful tool to screen for analogs of SEQ ID NO.5 in demonstrating that the analogs of SEQ ID NO.5 cause not only the same biological response as SEQ ID NO.5, but also cause the same response via the same mechanistic pathway, i.e. agonism of TLR9. Through use of the knockout mice according to the invention **(and only through the use of knockout mice according to the invention)** one of skill in the art has an assay to find mimics of SEQ ID NO.5 that will exclude compounds such as LPS and PGN. The importance of having such an assay is that it allows a medicinal chemistry program to make drugs for a specific target- i.e. TLR9, rather than other targets, allowing for greater control and predictability in the drug design process. As shown above, Example 4 provides evidence that SEQ ID NO.5 is an agonist for TLR9, while LPS and PGN are not agonists for TLR9, and therefore LPS and PGN can be excluded from further study in any program designed for TLR9 agonism.

With respect to a specific disease against which the potential therapeutic may be targeted, one candidate would be infection with *Leishmania major*, the cause of leishmaniasis. According to the World Health Organization website, leishmaniasis is a potentially lethal

infection that currently threatens up to 350 million people worldwide in 88 countries. American soldiers in Iraq afflicted with leishmaniasis refer to the disease as "Baghdad boil". While treatments for leishmaniasis are available, fundamental research into leishmaniasis continues in order to design better (i.e. more rapid, cheaper, more effective, fewer side effects, etc.) treatments. For example, attached herewith is a copy of Zimmerman et al., "Cutting Edge: CpG Oligodeoxynucleotides Trigger Protective and Curative Th1 Responses in Lethal Murine Leishmaniasis," *Journal of Immunology*, vol. 160, 3627-3630, 1998. Zimmerman reports that treatment of infected mice with a nucleotide sequence identical to SEQ ID NO.5 provides a protective and curative response in the mice. Zimmerman reports that SEQ ID NO.5 was "even curative when given as late as 20 days after lethal *L. major* infection," (see Zimmerman, abstract, lines 10-13). While Zimmerman shows that SEQ ID NO.5 is curative of otherwise lethal *L. major* infection, SEQ ID NO.5 may have other properties that make it an inappropriate or expensive drug for administration to humans. It is a well-established practice in medicinal chemistry to continue designing better drugs to replace compounds that are shown to work. As part of that research, it is important to have an assay to show that the new putative drugs operate not only with the same result, but also through the same mechanism. Knockout mice according to the invention are important in assays of new putative therapeutics. Based on the results in Example 4, one of skill in the art has evidence to exclude LPS and PGN from a program screening for compounds that cure or treat *L. major* infection via the same mechanism as SEQ ID NO. 5. Similarly, an unknown compound can be tested in an assay according to Example 4 in order to determine whether or not to take the compound into the next round of assays, saving both time and money for researchers looking for new treatments of *L. major* infection.

It is a well-established principle that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Therefore, the present application need not teach, and preferably omits, the fact that SEQ ID NO.5 was already known in the art as early as Zimmerman's 1998 publication date for its anti-*Leishmania major* properties.

The utility of the knockout mice and cells according to the invention for screening treatments against bacterial infection such as *Leishmania major* is specific, substantial and credible. In the same way that research tools such as microscopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds), the knockout mice and cells according to the invention have clear, specific and unquestionable utility in screening for putative analogs of SEQ ID NO.5 for the treatment of bacterial infection such as *Leishmania major*.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 35 and 38 are rejected under 35 U.S.C. § 112, first paragraph, for failing to enable one skilled in the art for "using the claimed animals and practicing the claimed screening methods," (Office Action, page 8, lines 3-5). Applicants respectfully traverse.

Legal Standard for Enablement

The legal standard for enablement is that a deficiency under the utility prong of 35 U.S.C. § 101 also creates a deficiency under 35 U.S.C. § 112, first paragraph. See *In re Brana*,

51 F.3d 1560 (Fed. Cir. 1995); *In re Jolles*, 628 F.2d 1322, 1326 n.10 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243 (CCPA 1971) ("If such compositions are in fact useless, appellant's specification cannot have taught how to use them.").

Enablement in Screening for Agonists of TLR9

As discussed above, Experiment 4 provides a specific example of screening for agonists of TLR9 which can be useful in the treatment of bacterial infection (see page 21, line 26 through page 23, line 29). In the example, the specification compares the response of cells from wild-type and knockout mice according to the invention to SEQ ID NO.5, as shown in Figure 5. The results show that the wild-type and knockout cells respond differently to SEQ ID NO.5, which shows that SEQ ID NO.5 is an agonist for the receptor that is lacking in the knockout animal. The example also shows that wild-type and knockout cells "produce almost the same" response to LPS or PGN (see Figure 5). In other words, Example 4 demonstrates a screen for agonists of TLR9, and shows that SEQ ID NO.5 is an agonist of TLR9, while LPS and PGN are not agonists of TLR9. In the same fashion, the knockout mice and cells according to the invention are useful for screening additional putative agonists for TLR9 in a medicinal chemistry program for treatments of bacterial infection that would operate via the same mechanism as SEQ ID NO.5, as shown in Experiment 4.

It is known in the art to use SEQ ID NO.5 against *L. major* infection (see Zimmerman cited above). Therefore, one of skill in the art with the instant specification (see Experiment 4) in hand would be enabled for screening additional treatments against *L. major* infection using the knockout mice and cells according to the invention. For example, the specification in Example 4 clearly shows that LPS and PGN do not have the same mechanism as

SEQ ID NO.5, and therefore, could be excluded when screening for compounds with the same mechanism as SEQ ID NO.5.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 14119.105010. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 14119.105010.

Respectfully submitted,
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